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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/225,478	04/08/94	KOHN D	

18N2/0203

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ART UNIT	**PAPER NUMBER**
1819	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE

Office Action Summary	Application No. 08/225,478	Applicant(s) Kohn et al.
	Examiner Brian R. Stanton	Group Art Unit 1819

☒ Responsive to communication(s) filed on *Oct 30, 1997* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-26* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-26* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1819.

The response filed 10/30/97 (Paper No. 32) has been entered. Claims 1-26 remain pending in the instant Application.

The indication that the pending claims are considered to be free of the prior art is hereby WITHDRAWN in favor of the newly advanced rejections under 35 U.S.C. 103 advanced hereinbelow.

Claim Rejections - 35 USC § 112

Claims 1-5 and 16-22 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to methods of treating severe combined immunodeficiency syndrome using therapeutic gene transfer to autologous CD34+ cell obtained from cord blood cells wherein said cells have been genetically engineered with a nucleic acid encoding adenosine deaminase (ADA) and further wherein said cord blood cells are administered to a patient such that said ADA encoding nucleic acid is expressed in an amount sufficient to provide a therapeutic effect, does not reasonably provide enablement for the treatment of any and all diseases with any and all cells and nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is maintained for reasons of record advanced in the preceding Office Action mailed 5/28/97 (Paper No. 29). Applicant's arguments filed 10/30/97 (Paper No. 32) have been fully considered but they are not persuasive.

In the amendment filed on 10/30/97, applicant has amended claim 1 to deleted the recitation that the administered cells are required to express an effective amount of a therapeutic protein. Therefore, as amended, claim 1 now fails to recite a process critical to what is claimed.

Applicant argues that they have demonstrated the principle that one may engineer autologous CD34+ cells as claimed and that they need not demonstrate all embodiments within the scope of what is claimed. In this regard, applicant argues that since they have demonstrated that ADA can be expressed in human cells, one would have expected that their methods would function in combination with any gene. Applicant further urges that given the instant specification and associated evidence that the burden is on the examiner to show why the claimed methods would not have been expected to have functioned in combination with other genes. However, it is believed that this burden has been met. Specifically, in the prior Office Action (Paper No. 29) it was noted on page 7 that Kohn et al., 1995 supported the conclusion that further work was required to establish *in vivo* gene for other genes. An additional reference supporting this position is now cited. In a review of the gene therapy art and clinical trials by a National Institutes of Health review panel, it was concluded that it was necessary to rethink the possibilities and potentialities of gene therapy. In the "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" that took place on December 7, 1995, the panel found, among others that:

> 1....The types of disease under consideration for gene therapy are diverse; hence many different treatment strategies **are being investigated, each with its own set of scientific and clinical challenges**.
>
> 2. While the expectations and the promise of gene therapy are great, **clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol**, despite anecdotal claims of successful therapy and the initiation of more that 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.
>
> 3. **Significant problems remain in all basic aspects of gene therapy**. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host.
>
> ...
>
> 7. Overselling of the results of laboratory and clinical studies by investigators and their sponsors--be they academic, federal, or industrial---has led to the mistaken

> and widespread perception that gene therapy is further developed and more successful than it actually is. Such **inaccurate** portrayals threaten confidence in the integrity of the field and may ultimately hinder progress toward successful application of gene therapy to human disease.

(emphasis added; see reference at pages 1 and 2). This report continues on the ensuing pages to report on the basis of their conclusions. Thus, in contrast to applicant's assertions to the contrary, at the time of the invention and continuing to at least 1995, the artisan did not accept that gene therapy was established such that one could have practiced any treatment methods for any particular disease in the absence of specific and particular guidance. While the prior art did not specifically address the methods instantly claimed, the issue of garnering *in vivo* gene therapy by any means was considered sufficiently unpredictable that, in the absence of evidence to the contrary, the artisan would not have accepted that one could have extended the single set of results evidenced in the instant application to results that would have been expected using other genes and treatment methods. Therefore, the limitations set forth in the statement of the instant ground of rejection remain appropriate.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al., 1992, Moritz et al., 1993 and Kohn et al., 1992 (all previously cited), the preceding combination in view of either or Boyse et al., 1993 or Moore et al., 1993 (the latter two references newly cited). This rejection is maintained essentially for reasons of record advanced in the preceding Office Action mailed 8/21/95 (Paper No. 10) with the exception that the newly cited prior art is now made of record to rebut applicant's arguments advanced in the previous response filed 11/12/96 (Paper No. 16).

The claimed invention is drawn to method of gene therapy wherein CD34+ cells obtained from cord blood is used as a host for *in vitro* transfection with a therapeutic gene following by reintroduction of the resultant recombinant cells into a host. In particular embodiments of what is claimed, an ADA gene introduced into CD34+ cells to treat severe combined immunodeficiency syndrome.

Anderson (1992) discusses the concerns of transducing only mature cells and not stem cells (CD34+ stem cells) in their existing protocols (see e.g. page 811). Anderson also discloses that the ability of progenitor cells to continuously express a gene that has been integrated into their genome would be beneficial for the purpose of expressing ADA. Anderson differs from the claimed invention in that the reference fails to disclose the use of cord blood derived CD34+ cells.

Moritz et al. disclose the use of cord blood cells due to their large fraction of primitive progenitor cells.

Kohn et al. disclose the increase in percentages of transduced CD34+ cells when said cells are cultured in the presence of growth factors such as IL-3, IL-6, and c-kit ligand.

In the response filed 11/12/96, applicant argued that the preceding combination of referenced failed to disclose the use of cord blood derived CD34+ cells and therefore the claimed invention would have been non-obvious. However, the newly cited prior art remedies this deficiency in the teachings of the cited prior art.

Specifically, Boyse discloses that "neonatal hematopoietic stem and progenitor cells can be obtained from umbilical cord blood and/or placental blood" (see column 13, lines 5-9) and that such stem cells can be enriched for using a variety of techniques (see e.g. column 20, lines 14-31).

Also disclosed is that such cells may be expanded *in vitro* (see e.g. column 22, lines 34-53). It is also disclosed that stem cells may be used in gene therapy applications (see e.g. column 62, claims 36-46).

Moore et al. disclose the *ex vivo* expansion and gene therapy using cord blood CD34+ cells and the specific expansion of cord blood progenitor cells (see e.g. abstract).

Thus, the difference between the prior art and what is claimed is founded on the sources of the stem cells used in the claimed methods. However, it was recognized that hematopoietic stem cells could be isolated and expanded from cord blood. It is noted that in the absence of a showing that cells of different origins are distinct, the known use of a known cell would be considered as *prima facie* obvious. Therefore, the use of cord blood derived stem cells in the claimed methods would have been obvious to one of ordinary skill in the art at the time the invention was made because one would have expected that cord blood would have been a useful source of hematopoietic stem cells.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian R. Stanton whose telephone number is (703) 308-2801. The examiner can normally be reached on Monday to Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Brian R. Stanton, Ph.D.
January 26, 1998

BRIAN R. STANTON
PRIMARY EXAMINER
GROUP 1800